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Benefits of progestin contraception in non-allergic angioedema

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Summary

Background Hereditary angioedema attacks can be induced or worsened by oral contraceptive containing oestrogens.

Objectives The purpose of this study was to assess the impact of progestin contraceptives on angioedema attacks.

Methods We conducted a French retrospective, multi-centre study of progestin contraception in women with non-allergic angioedema, including hereditary angioedema type I, II and III and idiopathic angioedema. Patients were classified into four groups according to frequency of attacks. We evaluated the effects of progestin on the mean number of attacks and compared the number of patients in each group before and under progestin contraception. The influence of hormonal factors on the course of angioedema was also assessed.

Results Fifty-five women were included: mean age was 32.1 years (16–52) and mean follow-up 32.4 months (SD:29). Fourteen women were classified as type I (25.4%), two as type II (3.6%) and 19 as type III (34%) and 20 were idiopathic (36%). Seventeen patients were taking a low dose progestin-only pill (POP), 24 antigonadotropic progestins (AGP) and 14 both successively. Total or partial improvement was observed in 81.8% (45/55) of the patients and more frequently in those on an AGP agent (34 patients, 89.5%) than on POP (19 patients, 61.3%) ($P = 0.013$).

Conclusions & Clinical Relevance This is the first study evaluating the interest of antigonadotropic progestin contraception in a series of women with non-allergic angioedema. Progestins, especially antigonadotropic progestins, appear to convey a marked benefit in most cases. Antigonadotropic progestins could thus be recommended as adjuvant treatment in childbearing women with non-allergic angioedema.

Keywords C1 inhibitor, combined pill, estrogen, factor XII, IUDs, kinin, L Norgestrel IUD, progestin only pill

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Introduction

Hereditary angioedema (HAE) is characterized by recurrent, self-limited and unpredictable episodes of subcutaneous and submucosal swellings in any part of the skin as well as in the respiratory and gastrointestinal tracts. To date, HAE can be classified into one of three subtypes: types I, II and III. Types I and II are caused by mutations in the SERPING1 gene and associated with deficient levels of the C1 inhibitor (C1-Inh), a serpin (SERine Protease INhibitor) or dysfunctional C1-Inh [1]. The more recently identified type III HAE can be due to mutations in the Factor 12 (FXII) gene and was initially known as oestrogen-dependent (or sensitive) HAE [2–5]. This latter subtype has no, or only slight, alterations in the level or the activity of C1-Inh. It can be associated with a mild decrease in C1-Inh function (< 70%) under oestrogens and, in about 20% of the cases, a mutation on the FXII gene (Hageman factor) [6, 7].

C1-Inh limits C1 activation as well as blocking the Hageman factor and the pathways activated by its fragments – the kallikrein-kinin system and the fibrinolytic system – which are responsible for excessive release of bradykinin eventually resulting in increased vascular

permeability [1]. HAE attacks occur after bradykinin release following the activation of a step-by-step cascade, each step being a potential target for oestrogens as reported in various models [8–13]. In normal women receiving contraceptive pills, levels of factor XII, kinin-free high molecular weight kininogen and acetone-activated kallikrein were shown to be higher than those in a control group of women [14]. Despite no direct evidence that oestrogens are associated with contact system activation, these data strongly suggest that oestrogens can increase the release of bradykinin in women with HAE and thus worsen the attacks. Types I and II HAE are especially sensitive to endogenous or exogenous oestrogens [15–17]. Bork et al. have reported that the sensitivity to exogenous oestrogens is similar for the three types of HAE [15]. We also recently reported the effects of exogenous/endogenous oestrogens in a series of 26 women with type III HAE [7]. Alternative effective contraception is thus mandatory for these women.

Low dose progestin-only pills (POP) is the usual alternative to oestrogen-containing contraceptives for HAE patients with C1-Inh deficiency [18]. However, limited compliance observed in some series and their limited efficacy on reducing the frequency of attacks suggest the need for another type of contraception [19–21]. Increasing the dose of the progestin agent results in an additional antigonadotropic effect and thus improves contraceptive efficacy. We took advantage of the availability of a relative high number of progestin contraceptives in France to improve contraception tolerability in women with HAE. Providing both an effective contraception with good compliance and a hypoestrogenic environment could have a favourable effect on the course of HAE. In this study, we obtained information about the relation between the use of progestin contraceptives and the clinical manifestations of 55 women with recurrent angioedema and provide evidence that these agents significantly reduce the number of attacks in all the HAE types and in idiopathic AE.

Materials and methods

We conducted a retrospective analysis of non-allergic AE cases from the National Angioedema Reference Centre (CREAK) in France. A questionnaire was sent to the eight reference centres that form CREAK and which were involved in the management of AE in 2008–2009. The aim was to collect data about women with documented non-allergic AE, irrespective of the type, who were using any of the progestin contraceptives. The questionnaire was filled in by the patient's local MD.

When a potential patient was identified, she was systematically contacted by telephone by one of us (CS) to obtain informed consent to participate in the study and to confirm the content of the medical file. At the time of the study, this was the only requirement regarding retrospective analysis of pre-existing data according to French law.

We collected clinical data (family history, frequency, duration and site of the attacks before and when using progestin contraception, age at onset, oestrogen sensitivity, that is, the influence of puberty, exogenous oestrogens and pregnancy on the attacks), laboratory results (C1-Inh protein antigenic level and function, C4, C3), genetic investigations (SERPING1 and FXII genes) and therapeutic management for all of the patients. Patients were classified as type I or II according to the C1-Inh values, presence of mutations and family history. Type III AE is defined as a clinical history of AE with normal levels of C1-Inh and a possible decrease in its function under oestrogens, a gain-of-function mutation of Factor XII Hageman and/or a worsening of the clinical symptoms under oestrogens and a family history. Women with the same clinical symptoms but no factor XII Hageman mutation and no family history were considered having idiopathic AE.

We focussed on the history of hormonal modulation of the attacks and contraception used. Some of these have been previously reported but without any specific reference to the progestin contraception.

In the absence of any validated severity score for AE, patients were classified according to the frequency of their attacks irrespective of the severity: Group 1 included women who presented less than one attack per month; Group 2 an average of one attack per month; Group 3 more than one attack per month; and Group 4 one or more than one attack per week. We considered that the frequency of attacks can be taken as a marker of severity. Following progestin treatment, a group 0 was defined as patients who did not experience any attack for at least 1 year without any additional routine treatment than progestin.

The primary objective was to evaluate the number of attacks per year before and during progestin contraception. The secondary objective was to compare the effects of the two types of progestin, POP and stronger antigonadotropic agents (AGP), on the attacks.

The POPs included oral forms (L-norgestrel, norgestrienone and desogestrel), implants (desogestrel) and the L-norgestrel intrauterine device (IUD). Alternatively, women received an AGP including a nortestosterone derivative with androgenic potency, Lynestrenol (Lyn, 10 mg/day), a norpregnane derivative, nomegestrol acetate (Nomac, 5 mg/day), or a pregnane derivative, chlormadinone acetate (CMA, 10 mg/day). In most instances, POP was prescribed after a patient first consulted her gynaecologist. However, if the attacks persisted on POP, or if the patient first consulted a specialist in non-allergic AE, the choice of molecule

was based on the type of AE with the rationale that norsteroids at high doses (Lynestrenol or Norethisterone 10 mg/day) could be helpful in type I and II AE because of their mild androgenic potency. In the other cases, Nomac was prescribed as a stronger AGP agent, but with fewer potential side-effects than norsteroids, in women with hyperandrogenia, metabolic disorders or CMA according to the clinical profile of the patient. One molecule was switched to another one to improve clinical tolerability.

Routine treatment of AE was adapted to the clinical course during the progestin prescription. These consisted mostly of anti-fibrinolytic agents (e.g. tranexamic acid) or attenuated androgens (e.g. danazol): tranexamic acid was prescribed at 1 g/8 h to 1 g/4 h for moderate to mild attacks. A C1 inhibitor [Berinert® (20 U/kg IV) (CSL Berhing S.A., Paris, France) or Firazyr® (30 mg subcutaneous) (SHIRE France S.A., Boulogne-Billancourt, France)] was used for worsening or severe attacks (abdominal and laryngeal). We could not accurately evaluate modifications to routine treatment in this retrospective study because of recall bias. We considered the number of attacks to reflect the global evaluation of a patient's clinical status.

Statistical analysis

Results are presented as mean ± standard deviation (SD) for quantitative data and percentages for qualitative data. Comparisons between groups were performed using chi-square test for qualitative data with Yates correction when necessary. Statistical analysis was performed with R statistical software version 2.4.0 (http://marne.u707.jussieu.fr/biostatgv/).

Results

Of the 55 patients analysed, 14 had type I HAE (25.4%); two (3.6%) type II; 19 (34%) type III; and 20 (36%) idiopathic AE.

Genetic analysis had been performed for 10 of the 16 patients with type I or II HAE. A mutation in SERPING1 was observed in all of these patients. The remaining six women were classified as having type I or II based on a strong family history and classic pathology. FXII mutation was observed in 10 of the other patients. Type III is defined as AE with a mutation of FXII and/or a family history of AE and in this study concerned 19 patients. The rest of the patients (20) displayed no family history of AE or FXII mutations but a clinical history of AE, resistant to chronic antihistaminic treatment, sensitive to tranexamic acid and/or worsening under oestrogen-containing pill. They were considered being idiopathic in this study even though they could also be considered having sporadic type III.

The mean interval between the first symptoms and diagnosis was 7.9 years ± 7.6 (range 1–360 months).

Clinical characteristics of the patients

The median age was 31 years (range 16–52 years) and the mean (± SD) 32.1 years (± 9.74) (Table 1). The clinical characteristics are described in Table 1 among the various HAE types. There was a non-significant higher number of attacks in type III and idiopathic AE patients (Table 1). In addition, laryngeal attacks occurred at least as frequently in these patients as in the others (Table 1). Five patients presented with more rare localizations: two with arthritis or cephalalgia, one with vulvar oedema, one with pericarditis and one with bladder oedema. Twenty-five percent of the patients were classified in Group 1 (14/55), 31% (17/55) in Group 2, 20% (11/55) in Group 3 and 23.6%(13/55) in Group 4. Thus, almost half of the patients (25) could be considered severe. During their history of angioedema, 24/55 patients (43.6%) had experienced at least one stay in an emergency unit and four in an intensive care unit.

Influence of hormonal factors

Puberty. Fourteen patients either experienced their first symptoms or a worsening of attacks at puberty (25.4%): nine patients with type I (64.3%); one with type II, one with Type III (5%) and three of the 20 patients with idiopathic AE. The difference between types I/II and III+ idiopathic was significant ($P < 0.001$) (Table 2).

Pregnancy. Twenty-seven pregnancies occurred in 27 patients. Thirteen of these patients (48.1%) experienced

Table 1. Baseline clinical characteristics and frequency of attacks according to the type of AE

Attacks	HAE type I ($n = 14$)	HAE type II ($n = 2$)	HAE type III ($n = 19$)	Idiopathic AE ($n = 20$)
Abdominal *n* (%)	13 (92.8)	2 (100)	13 (68.4)	11 (55)
Subcutaneous *n* (%)	13 (92.8)	1 (50)	18 (94.7)	17 (85)
Laryngeal *n* (%)	7 (50.7)	1 (50)	11 (58.1)	14 (70)
Group 1	5	0	6	3
Group 2	6	2	4	5
Group 3	2	0	4	5
Group 4	1	0	5	7

HAE, hereditary angioedema.
Group 1: women who presented less than one attack/month.
Group 2: women who presented an average of one attack/month.
Group 3: women who presented more than one attack/month.
Group 4: women who presented one or more than one attack/week.
NS: $P = 0.08$ comparing frequency of attacks within Type I, Type III and idiopathic AE.

Table 2. Influence of hormonal factors on attack frequency according to type of AE

Hormonal factor	Type I/II HAE (n = 16)	Type III HAE (n = 19)	IdiopathicAE (n = 20)	P*
Puberty(n)	62.5% (10)	5% (1)	15% (3)	< 0.001
Pregnancy(n)	60% (6/10)	44% (4/9)	37.5% (3/8)	NS
COC(n)	55.5% (5/9)	73.7% (14/19)	66.6% (12/18)	NS

P-values were calculated for HAE type III and idiopathicAE combined. COC, combined contraceptive pills; HAE, Hereditary angioedema.

Table 3. Efficacy of progestin on attacks according to the progestin type

Frequency of attacks	AGP	POP	Total
Improvement	34	19	53*
Increase or no modification	4	12	16*
Total	38	31	69*

AGP, antigonadotropic progestin agents POP, Low dose progestin-only pills.
*Number of progestin treatments used.

worsening of the disease during their pregnancy (6/10 types I+II (60%) vs. 4/9 type III (44%) and 3/8 (37.5%) (NS), whereas 22.2% experienced an improvement and 30% no change.

Combined Estrogen-progestin contraception. Forty-six of the patients used combined contraceptive pills (COC). For 31 of them (67.4%), COC induced (10 patients) or worsened attacks (21 patients): 55% in women with type I (5/9), 73.7% women with type III (14/19) and 66.6% with idiopathic AE (12/18) (NS). However, it is important to note that women with HAE I/II received a COC prescription less often since they were diagnosed at a younger age than women with type III.

Effect of progestins on frequency of attacks

The mean follow-up under progestin contraception was 32.4 ± 29 months (mean ± SD) (Table 3 and Fig. 1). Overall, progestin agents reduced the frequency of attacks in 45 (81.8%) patients. Twenty (36.3%) remained free of symptoms for a mean duration of 18.3 months ± 17.5 (range 3–72 months) and did not use any medication other than the progestin. Eleven of these patients previously used a daily AE treatment which was then stopped. Twenty-five (45.4%) patients improved and were classified in a less severe group while on progestin contraceptive (Fig. 1). This improvement was seen for all kinds of attack and AE type (Table 4). Among them, twelve patients were still on a chronic prophylactic treatment combined with progestin, mostly tranexamic acid and only one patient still used danazol. Progestins

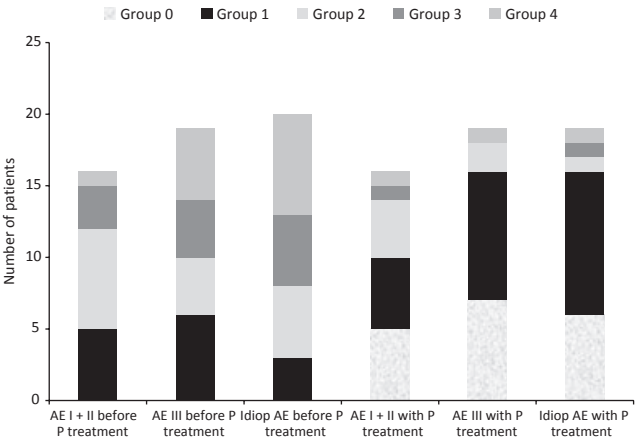

Fig. 1. Frequency of the attacks according to the type of AE before and on progestin. Group 0: No attacks during the follow-up. Group1: women who presented less than one attack/month. Group 2: women who presented an average of one attack/month. Group 3: women who presented more than one attack/month. Group 4: women who presented one or more than one attack/week. Hereditary angioedema: hereditary angioedema. P: progestin.

Table 4. Efficacy of progestin according to type of HAE

		POP	AGP
AE types I/II	Improvement	5	6
	No modification	2	1
	Worsening	1	0
AE type III	Improvement	10	13
	No modification	1	2
	Worsening	2	0
IdiopathicAE	Improvement	4	15
	No modification	2	1
	Worsening	4	0

POP, Low dose progestin-only pills; AGP, antigonadotropic progestin agents; HAE, Hereditary angioedema.

had no effect on the frequency of attacks in seven patients (12.7%).

Efficacy varied according to the type of progestin administered (Table 4). Forty-one patients received only one type of progestin. Among them, 24 received an AGP and 17 a POP. The other 14 patients were successively treated by the two types of treatment. Among the 38 patients who had been prescribed an AGP, 34 (89.5%) improved whereas only 19 patients (61.3%) of the 31 who took a POP improved: this difference was significant (P = 0.013). Moreover, seven patients worsened (22.6%) while taking POP (oral desogestrel in three patients, levonorgestrel in one and L-Norg IUD in three) and none on AGP. In the fourteen patients who had taken both treatments, four patients worsened with POP but none with AGP (Table 4).

We then looked at whether the individual sensitivity to hormonal factors could predict the clinical response

to progestin. Eighty one percent (17/21) of the patients in whom puberty or pregnancy had a triggering effect improved using progestins and 78.5% (22/28) of the women whose disease was not triggered by these hormonal factors also improved. Eighty-six percent (26/30) of the patients whose condition worsened on COC improved on progestins and 80% (12/15) of patients for whom COC had no effect on their symptoms improved. Overall, this suggests that progestins may be effective irrespective of the previous individual sensitivity to hormonal factors.

Safety of the treatment

There was no record of serious adverse events related to the progestin: no thromboembolic events or liver toxicity and no unwanted pregnancy. Mild adverse effects occurred in 17 patients (30.9%) and consisted mostly of weight gain (five patients), symptoms of oestrogenic deficiency (4), breakthrough bleeding (2) and hyperandrogenia (2). In most of the cases, the adverse effect resolved following a switch to another progestin agent.

Six patients previously using danazol discontinued treatment for hyperandrogenia or a severe side-effect in two cases (1 venous thrombosis and 1 pancreatitis).

Discussion

In this retrospective study, we show that AGP agents can be effective in the chronic management of women with any type of non-allergic AE by decreasing the frequency of the attacks. In addition, they are well tolerated and constitute an effective contraception.

HAE is a rare disease which occurs in young active women and is associated with life threatening events and frequent disability contributing to considerable disease burden and negatively effecting quality of life [22]. It is thus of utmost importance to find therapeutic options which could help these patients. Our study suggests that modulation of endogenous oestrogen by progestins may help to control the attacks in most patients.

HAE patients are known to be extremely sensitive to endogenous or exogenous oestrogens irrespective of the type of HAE [5, 15–17, 23]. These observations led to the recommendation via expert consensus that oestrogens should be avoided when possible in HAE patients with C1-Inh deficiency [24, 25]. The contraceptive pill can worsen attacks in 60–80% of the patients with HAE type I/II [6, 16]. Only two studies have so far reported the effects of COC in series of women with HAE type III, respectively, on 39 and 26 women [6, 7]. In our series, we also found that COC triggered or exacerbated the symptoms in two thirds of the women irrespective of the type of AE. The rationale for the oestrogen worsening effects on AE attacks might be connected with their influence on bradykinin production through most steps of the cascade [8–14]. Oestrogen can act by lowering C1-Inh levels and modulating FXII gene transcription through oestrogen responsive element sequences on the promoter [10–12]. They can also modulate the kallicrein/kinin cascade, induce bradykinin type II receptor expression and enhance bradykinin action [8, 9, 26].

A possible alternative to COCs in women with AE are progestin contraceptive agents. The progestins used world-wide in this setting are the POP minipills, IUDs or injectable medroxyprogesterone acetate (MPA) [27, 28]. However, in France MPA is reserved for patients with extreme compliance difficulties related to psychiatric because of poor tolerability and possible side-effects [29]. Furthermore, while POPs are widely prescribed as an alternative to COCs in women with AE, they have limited efficacy and tolerability [20, 21]. Small French series and a larger European survey have reported on the limited beneficial effects of POP in patients with type I-II HAE [16–18, 30].

We studied the effects of both POPs and AGPs in women with type I, II or III HAE and idiopathic AE and found the AGP agents to be more effective. This is consistent with other studies reporting varied improvement with POPs and may be due to differences in antigonadotropic activity. Bork et al. reported marked benefits of POP or MPA in eight women in type III HAE with FXII mutations [6]. Several other molecules with a range of antigonadotropic potencies are available and were used in the women we studied in this series to improve efficacy and tolerability of their contraception. Norethisterone derivatives (lynestrenol and norethisterone acetate at 10 mg/day) are potent antigonadotropic and anti-oestrogen agents and mild androgens. Although they represent a useful treatment option in women with HAE due to their androgenic potencies, their use is limited in some patients because of metabolic and clotting adverse effects [31]. However, these effects are milder than with attenuated androgens [32]. Norpregnane and pregnane derivatives have relatively strong antigonadotropic properties but, apart from MPA, are not androgenic. Pregnane derivatives provide a lower risk of metabolic and vascular complications and their use has been validated in women at specific risk under COC including those at high risk of venous thrombosis [33–35]. POPs contain low doses of progestin derived from 19 nortestosterone. Because of their low dosage, antigonadotropic inhibition with POP is incomplete and variable from one patient to another. It results in functional cysts in about 30% of women creating hyperoestrogenism conditions [20]. This hyperestrogenism could explain the absence of improvement or even in some cases the exacerbation of the attacks. On the other hand, in addition to lowering circulating estradiol levels, AGP could also directly act on the

Table 5. progestin used as contraceptives which can be used in women with HAE

Progestin	Molecules	Dose	Sequence of administration		Brand names
Normethyltestosterone					
Antigonadotropic dose	Lynestrenol*	10 mg/ days	17–21 days/28	Continuous	Orgametril
	Norethisterone acetate*	10 mg/ days	17–21 days/28	Continuous	Primolut Nor/Utovlan
No longer available	Ethynodiol diacetate*	8 mg/ days	17–21 days/28	Continuous	Lutometrodiol
Moderate dose ("POP")	Norethisterone/ Norethindrone acetate	300 μg/ days		Continuous	
	LNorgestrel	30 μg/ days		Continuous	Microval/ Norgeston
No longer available	Norgestrienone	350 μg/ days		Continuous	Ogylline
	Desogestrel	75 μg/ days		Continuous	Cerazette
Implant	Desogestrel	68 mg		Continuous 3 years	Nexplanon/Implanon
	LNorgestrel	6 × 36 mg		Continuous 5 years	Norplant
IUD Norgestrel	LNorgestrel			Continuous 5 years	Mirena
Pregnanes					
	Medroxy progesterone acetate*			Injectable 3 months	Depo Provera
	Chlormadinone acetate*	10 md	21 days/28		Lutéran
Norpregnanes	Nomegestrol acetate*	5 mg	21 days/28		Lutényl

*Especially recommended in women with HAE according to our results (MPA was not used in this study but due to its androgenic potency and availability in most countries it might be recommended).

bradykinin cascade as reported. It has been shown that progestin can inhibit the estradiol effects on bradykinin mediated vasodilatation or modulate some kininase levels [36, 37]. The indication of progestin in our study was mainly as an alternative to COC. POP was the first-line progestin for most of the women but some had been prescribed an AGP agent in first line if they were recently diagnosed in a specialized centre.

We also studied the relation with hormonal sensitivity and found that the benefit of progestin treatment was not directly related to previously observed sensitivity to other hormonal factors. In our series, onset of HAE with C1-Inh deficiency occurred more often before puberty than in patients with type III or idiopathic AE. In effect, only a minority of patients with type III HAE were symptomatic before puberty. Similarly, Bork et al. reported that cases of type III HAE are rarely observed before puberty [38]. Our results also confirm previous reports of the unpredictable effect of pregnancy in women with HAE [1, 6, 7, 16, 38].

Clinical symptoms were equally distributed between classic C1-Inh deficiency or dysfunctional types, type III and idiopathic AE. Interestingly, the disease was at least as severe in women with type III HAE and idiopathic AE as in those with types I and II.

The following limitations and strengths of the study deserve to be mentioned. The main limitations are inherent to its retrospective design. For example, we were not able to confirm the causality between use of progestin and improvement of the patients. However, it was a multi-centre, nation-wide study evaluating data collected by a national reference centre and demonstrates for the first time the advantage of AGPs over POPs in women with HAE. A prospective study is now necessary to confirm the benefits and the magnitude of the benefits they convey on patients with non-allergic AE. Another drawback of our study is that we used progestins that are not easily available in all countries which may limit the generalization of our findings. We have, however, included Table 5 to help clinicians identify which molecules they could use in their patients according to availability in their country.

Conclusion

AGP agents are well tolerated and effective in patients with symptomatic non-allergic AE. They could constitute a reliable adjuvant treatment option as well as providing effective and well-tolerated contraception in these patients for whom pregnancy has to be programmed.

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Conflict of interests

All the authors except C. Saule and G. Plu-Bureau are members of the Advisory board of Shire France for that received consulting fees and of the Advisory board of Behring France.

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